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ASSOCIATION OF SMOKING AND SEVERITY OF COVID-19 INFECTION AMONG 5889 PATIENTS IN MALAYSIA: A MULTI-CENTRE OBSERVATIONAL STUDY

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Highlights

- Smoking affects the immune system and health of the smokers.
- Smoking increased the risk of getting severe COVID-19 infection.
- Smokers had higher risk of getting COVID-19 complications.
- COVID-19 brings opportunity to highlight the benefits of quit smoking.

ABSTRACT

Objective: This study aims to investigate the association between smoking and the severity of COVID-19 infection during the initial wave of this pandemic in Malaysia.

Methods: This is a multi-centre observational study using secondary hospital data collected retrospectively from 1st February 2020 until 30th May 2020. Clinical records of all real-time polymerase chain reaction (RT-PCR) confirmed COVID-19 cases with smoking status, co-morbidities, clinical features and disease management were retrieved. Severity was assessed by presence of complications and outcomes of COVID-19 infection. Logistic regression was used to determine the association between COVID-19 disease severity and smoking status.

Results: A total of 5889 COVID-19 cases were included in the analysis. Ever smokers had higher risk of having COVID-19 complications such as acute respiratory distress syndrome (OR: 1.69, 95% CI = 1.09 - 2.55), renal injury (OR: 1.55, 95% CI = 1.10 - 2.14) and acute liver injury (OR: 1.33, 95% CI = 1.01 - 1.74) compared to never smokers. However, in term of disease outcomes, there were no differences between two groups.

Conclusion: Although no significant association was found in term of disease outcomes, smoking is associated with higher risk of having complications due to COVID-19 infection.

Keywords: Smoking, COVID-19, severity, complications, disease outcome, Malaysia

1. Background

Coronavirus is a large family of viruses that can infect both animals and humans. In humans, several coronavirus are known to cause respiratory infections ranging from common cold to a more severe disease such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (WHO, 2019). The most recently discovered coronavirus is known as SARS-CoV-2 that was reported in Wuhan, Hubei Province, China, in December 2019. This virus spread worldwide extremely fast evolving into a pandemic that affected many countries. In Malaysia, the first wave of COVID-19 epidemic began in late January whereby only 22 confirmed cases were reported (Ng et al., 2020). The second wave of infections broke out in late February 2020 and grew rapidly in the first 3 weeks, where Malaysia reported three digit cases in a day. By the end of August 2020, 9340 confirmed cases were recorded. Malaysian's Prime Minister announced a nationwide Movement Control Order (MCO) that went into effect on March 18, 2020. The main aim was to reduce social mixing and approximately 3 weeks after the MCO, disease transmissibility (R_t) had reduced substantially from 3.1 to 1.0 and remained below 1.0 for the remaining period (Ng et al., 2020). However, in October 2020, Malaysia entered the third wave of COVID-19 and up until 16th April 2021, there were about 370,528 cases with 1,365 deaths reported.

Smoking is one of the biggest causes of illness and contributed to 8 million deaths around the world. Both smoking and COVID-19 infection affect primarily the respiratory system. In Malaysia, the burden of smoking remains high where the prevalence of smokers among adults

aged 15 years and above was 21.3% (National Health and Morbidity Survey, 2019) and among adolescents aged 13-15 years was 13.2% (Adolescent Health Survey, 2017). Smoking harms nearly every organ of the body, causes many diseases, and reduces the health of smokers in general. Smokers may already have lung disease or reduced lung capacity which would greatly increase risk of serious illness. In respiratory diseases, when a person smokes, evidences have shown that the chance of getting infection is higher and the infection is more severe (van Zyl Smit et al., 2010). The respiratory diseases are due to tobacco smoke which causes the deposition of particles in the airways and damages the protection mechanisms of the respiratory system at different levels, alters the function of the ciliary mucus and the clearance of inhaled substances. It also enables the adherence of microorganisms to airway epithelial cells, increases alveolar permeability and decreases cellular and humoral immunity (Feng et al., 2011; Murin and Bilello, 2005). Smoking also affects the immune system and its respond to infection, making smokers more vulnerable to infectious diseases (Zhou et al., 2016). Through these effects on the immune system, smoking may facilitate influenza virus infection, its severity, and its most frequent complications, such as pneumonia (Almirall et al., 2008; Epstein et al., 2010). Previous studies have shown that smokers are twice more likely to contract influenza, presented with more severe symptoms and had higher mortality rate in the previous Middle East Respiratory Syndrome coronavirus (MERS-CoV) outbreak (Park et al., 2018; Arcavi and Benowitz, 2004). Due to this, smoking is shown to be associated with poor prognosis, as most evidence highlighted the negative impact of tobacco use on lung health and its causal association with an abundance of respiratory diseases (Tonnesen et al., 2019).

In recent studies, researchers found that those with history of smoking had higher risk of getting severe COVID-19 progression compared to those who never smoked (Liu et al., 2020; Patanavanich and Glantz, 2020). A systematic review conducted in March 2020 concluded that

smokers were 1.4 times more likely to have severe symptoms of COVID-19 and approximately 2.4 times more likely to be admitted to an Intensive Care Unit (ICU), need mechanical ventilation or die compared to non-smokers (Vardavas et al., 2020). In addition, those with existing Chronic Obstructive Pulmonary Disease (COPD) and had ongoing smoking history were more likely to have worse progression and outcome of COVID-19 (Zhao Q et al., 2020). As COVID-19 pandemic is still a rapidly evolving topic and major health concern around the world, data on clinical characteristics of the patients, risk factors and prognostic factors are still scarce especially studies outside China (Khot and Nadkar, 2020). Current analysis remains limited due to the quality of primary data, although, early results indicate an association between smoking and COVID-19 severity (Grundy et al., 2020). In Malaysia, high smoking prevalence among both adults and adolescents creates a major burden on the healthcare system. Thus, there is a need to further strengthen the tobacco control policies and their implementation. Findings from this study will provide scientific evidence on the association of smoking and COVID-19 and also address on the limitation of the data availability. Therefore, this study aims to determine the association of smoking and severity of disease among the patients infected with COVID-19 in Malaysia.

2. Methods

2.1. Study design

This is a multi-centre observational study using secondary data from 18 COVID-19 designated hospitals in Malaysia. The data was collected retrospectively during the initial wave of COVID-19 pandemic in Malaysia which was from 1st February 2020 until 30th May 2020. Data used for this study have been verified and validated as reported in the study by Sim et al. (2020). The list of hospitals involved in this study is shown in the supplementary Table 1.

2.2. Inclusion and exclusion criteria

Patients included in this study were those aged 12 years and above who had been diagnosed with COVID-19 by laboratory confirmation of reverse-transcriptase-polymerase chain reaction (RT-PCR) analysis using nasopharyngeal and/or oropharyngeal swabs, tracheal aspirates, sputum or serum samples at designated National Public Health Laboratories, Institute for Medical Research, and accredited hospital laboratories. They were hospitalized in 18 designated COVID-19 hospitals in Malaysia and were followed up until they had completed outcome which was either discharged alive or dead.

2.3. Disease staging and clinical management

All COVID-19 cases admitted to the hospital were managed according to COVID-19 Management Guideline in Malaysia by the Ministry of Health. During this period, all cases were admitted for 14 days, or until free of SARS-CoV-2 carriage on repeated nasopharyngeal/oropharyngeal swabs, or death ensued. The clinical staging for patients presented with COVID-19 is shown in Table 1.

2.4. Study variables and outcome of interest

All COVID-19 patients were grouped according to their smoking status either ever smoker or never smoker. Ever smokers are defined as patients who reported as active smokers and former smokers while never smokers are patients who reported as never smoked any cigarette throughout their entire life. Active smoker was defined as those reported currently using any smoked tobacco products such as manufactured cigarettes while former smoker was defined

as those reported as currently non-smoker but had previously smoked daily. However, due to the limitation in data collection, the duration of quitting for former smokers can't be determined.

Variables related to sociodemographic data, admission characteristics, clinical progression, laboratory and radiographic investigations, management and clinical outcome were analysed for associations with disease severity according to these two groups. Personal data included sex, age, history of smoking and comorbidities such as chronic obstructive pulmonary disease (COPD), cancer, hypertension and/or diabetes. Clinical data included initial symptoms, clinical presentation, vital signs, respiratory support, complications and disease outcomes. Severity of COVID-19 infection was assessed by presence of complications and outcomes of COVID-19 infection such as admission to the intensive care unit (ICU), requirement of invasive ventilator support and the final outcome whether patients survived or died.

2.5. Statistical analysis

Continuous variables with normal distribution were expressed as mean and standard deviation and analysed using independent samples *t*-test, while those with skewed distribution were presented as median (Q1, Q3) and analysed using Mann-Whitney *U* test. Categorical variables were presented as numbers (percentages) and analysed using chi-squared test or Fisher's exact test. Logistic regressions were used to analyse the association between smoking status (independent variable) with disease severity upon discharge (dependent variable). Variables from disease severity which were complications and outcomes were selected to be included in the logistic regressions, based on clinical justification and statistical reasoning from univariate analyses. Missing data were treated with listwise deletion in subsequent analyses. A two-sided $P < 0.05$ is considered as statistically significant. R version 3.6.3 was used for all analyses.

3. Results

3.1. Sociodemographic, clinical histories and disease staging

A total of 5889 COVID-19 cases were admitted to hospitals all over Malaysia during the study period. The detail characteristics of these patients were published in another study (Sim et al., 2020). Out of 5889 cases, 529 (9.0%) patients were current smokers, 262 (4.4%) were former smokers and 5098 (86.5%) were non-smokers. For this study, the current and former smokers were grouped together as ever smokers and non-smokers as never smokers. The median age of the COVID-19 patients in ever smokers group were slightly older compared to never smokers (36 vs 34 years, $p < 0.001$).

As shown in Table 2, COVID-19 patients in ever smokers group had significantly higher proportion of diabetes, cardiac disease and chronic pulmonary disease compared to never smokers but the finding is vice versa for patients with history of asthma. There was a significantly higher proportion of ever smokers with shortness of breath compared to never smokers. Other symptoms such as sore throat, nausea, vomiting, fever and myalgia were also significantly higher in never smokers.

At the time of presentation to the hospital, higher proportion of ever smokers were classified as COVID-19 Stage III, Stage IV and Stage V compared to never smokers. Further sub-analysis among Stage III to Stage V COVID-19 patients demonstrated that the median age for ever smokers was significantly lower than that for never smokers (44 years old vs 52 years old, $p < 0.001$).

3.2. Physical examination at admission and investigations conducted to COVID-19 patients

For physical examination, higher blood pressure was observed in ever smokers while pulse rate and temperature were slightly higher in the never smokers (Table 3). Ever smokers had significantly higher mean white blood cells count, neutrophil count, hemoglobin, hematocrit and ALT level compared to never smokers. However, higher proportion of never smokers had high C-reactive protein more than ≥5mg/dl and lymphopenia. Mean lactate dehydrogenase (LDH) level was also higher in never smokers. Although not statistically significant, higher percentage of ever smokers had abnormal chest x-ray findings at the time of presentation.

3.3. Complications and outcomes of COVID-19 infection

In Table 4, ever smokers had significantly higher percentage of having complications of COVID-19 infection which were acute liver injury, renal injury, acute respiratory distress syndrome (ARDS), deep vein thrombosis and seizures. Higher proportion of ever smokers were admitted to the intensive care unit (ICU) and required oxygen support but this was not statistically significant. There was no difference between types of ventilation received, worst diagnosis and final outcome by both groups.

Based on logistic regression analysis (Table 5), in terms of complications, ever smokers had higher odds of having liver injury, acute renal injury and acute respiratory distress syndrome. For disease outcome, there was no statistically significant difference between ever smokers and never smokers. Subgroup analysis was carried out between current, former and non-smokers (Table 6). When compared to current smokers, former smokers had significant higher percentage of having liver and renal injury. In term of disease outcomes, higher percentage of former smokers were being admitted to ICU and required invasive ventilation compare to current smokers. Comparison between current and non-smokers however showed no significant

differences between these two groups. The odd ratios are shown in supplementary Table 2. Further analysis also found no significant association between smoking status with disease complications and outcomes when other variables such as age, gender and ethnicity were controlled.

4. Discussion

To the best of our knowledge, this is the first study to determine the association between smoking and COVID-19 severity among laboratory confirmed COVID-19 patients admitted to nationwide hospitals in Malaysia. The COVID-19 severity was assessed in term of complications and disease outcomes. The sample size for this study is much larger than other similar COVID-19 and smoking-related studies that reported sample size ranging from 41 to 1,099 (Zhou et al., 2020; Zhang et al., 2020; Huang et al., 2020 and Liu et al., 2020). Out of a total 5,889 COVID-19 cases admitted to the hospitals, majority (86.5 %) were non-smokers and the remaining (13.5 %) had a present or past history of smoking.

The prevalence of current smokers (9%) among COVID-19 patients found in this study was lower compared to the national data which was 21.3% (National Health and Morbidity Survey, 2019). However, the prevalence of current smokers in this study was higher compared to that in China as reported by Zhou et al. (2020). A review from Gonzalez-Rubio et al., 2020 based on the analysis of data from studies in China, USA and Italy also showed lower prevalence of smoking among COVID-19 hospitalized individuals compared to the countries' general prevalence of smoking. Based on this observation, the authors concluded that current smoking had the protective effect on the likelihood of hospitalization. However, this review raised serious concerns, as discussed by Berlin and Thomas, 2020 which highlighted poor data collection

method on smoking status, under reporting of smoking status, no biochemical verification of smoking status especially among those claimed as non-smokers and differences in the population characteristics that were being compared, suggesting a systematic error that compromised the conclusions. For our study, data was based on hospital record that was documented by the healthcare personnel and smoking status was based on patient self-declaration upon admission to the hospital that most likely led to under reporting of smoking status among the COVID-19 cases in Malaysia.

In this study, current smokers and former smokers were grouped together as ever smokers. This is due to the limitation in our data on the detailed history of quit smoking duration among former smokers. According to the Malaysian Clinical Practice Guidelines (CPG) Treatment of Tobacco Disorder 2016, a smoker is considered as former smoker once he has successfully quit from smoking which is complete abstinence without even a single puff of cigarette for at least six months from the last cigarette smoked. Therefore, the data on history of smoking was incomplete and those patients who declared themselves as former smokers might not actually fulfill the definition of former smokers. The other important limitation is duration of smoking among smokers which was not assessed in this study. Patients who have been smoking for longer duration are more likely to have higher risk of complications than those who have been smoking for a shorter duration.

Among all COVID-19 patients, ever smokers were found to be significantly ($p < 0.001$) much older (36 years old) compared to the non-smokers (34 years old). Although statistically significantly different, median age of smokers is only 2 years older than never smokers, which may not have clinical significance. As reported in Sim et al. (2020) study, the majority of affected individuals in Malaysia during this study period were of younger age group. In contrast, studies from other countries such as China, Korea and Singapore reported a much older group of

cases between 40 and 63 years. The difference in the age distribution could be related to the cluster effect from 3-days religious gathering where majority of the participants were young males.

Ageing is an important factor that can affect the severity of diseases especially if the primary organ is the lungs since pulmonary capacity and function decrease as the person aged (Sharma and Goodwin, 2006). In smokers, combinations of age-related lung function reduction and existing lung damage due to smoking were important determinants that lead to severe respiratory problems. This was supported by studies that found the risk of any infection and complications were higher among the smokers (van Zyl Smit et al., 2010, Feng et al., 2011; Murin and Bilello, 2005) and elderly people (Gavazzi and Krause, 2002). Interestingly, this study found that among COVID-19 patients who presented with Stage III and above, the median age for ever smokers was younger compared to never smokers. This further supports the fact that smokers have higher risk of getting severe infection due to existing impairment in their lung function and capacity even though they are still young. Data from population study in United Kingdom also found consistent association between smokers and risk of developing symptomatic COVID-19 (Hopkinson et al., 2021). Another study from Bangladesh also reported strong association between smoking and COVID-19 severity (Mohsin et al., 2021).

Based on the COVID-19 daily report by the Ministry of Health Malaysia in 2020, majority of COVID-19 patients who died had at least one chronic non-communicable disease (NCD). This was later proven by the findings in the study by Sim et al. (2020) where underlying chronic diseases such as chronic pulmonary disease or chronic kidney disease had been identified as one of the important factors related to a more severe COVID-19 infection. In this study, a higher percentage of ever smokers had diabetes, cardiac disease and chronic pulmonary disease compared to never smokers. This finding was alarming because it shows that smokers

have multiple risk factors besides age and smoking status that can also cause them to have severe COVID-19 infection.

Upon presentation to the hospital, significantly higher percentage of smokers complained of shortness of breath and has more severe degree of COVID-19 infection. The presence of pneumonia was confirmed by abnormality findings on the chest x-ray which was noted to be higher in smokers even though it was not statistically significant. This finding is consistent with the findings from different studies conducted in China (Zhang et al., 2020; Guan et al., 2020).

In this study, the severity of the disease was evaluated by presence of complications and the disease outcomes. In terms of complications, three most common complications among all COVID-19 patients in Malaysia were acute respiratory distress syndrome (ARDS), acute liver injury and kidney injury (Sim et al., 2020). In this study, the risks for these three complications were significantly higher in ever smokers compared to the never smokers. Further analysis conducted between current and former smokers, those patients whom reported themselves as former smokers had higher risk of liver and renal injury compared to current smokers. These findings could possibly be due to the longer duration of smoking in former smokers than current smokers. Cigarette smoking is a known major risk factor for developing chronic diseases, such as chronic obstructive pulmonary disease, liver disease and several malignancies (Charatcharoenwitthaya et al., 2020). The risk of death from these conditions increases with increasing exposure to cigarette smoking, as measured by the number of cigarettes smoked daily and the duration of smoking (Jacobs et al., 1999).

Ever smokers also have a higher risk of deep vein thrombosis and seizure. Tobacco smoke contains many chemicals that are harmful not only to the lung but also to the other organs. At the same time, the chemicals in tobacco smoke also affect humoral-mediated immune response in humans (Piao et al., 2009). All these factors make the smokers more vulnerable to

developing severe complications if they have any kind of infections. In term of disease outcomes, this study found higher proportion of ever smokers admitted to the intensive care unit (ICU), required invasive ventilatory support and died compared to never smokers, although they were not statistically significant. In contrast, the study conducted by Kozak et al. (2020) found a statistically significant association between smoking and ICU admission and mortality amongst 226 patients in Toronto, Canada. Meta-analyses conducted by Zhao et al. (2020) using data from 7 studies (n=1726 patients) also found a statistically significant association between smoking and severity of COVID-19 outcomes amongst patients (odds ratio, OR: 2.0, 95% CI 1.3 – 3.1). A more recent observational study with large sample size supports the causal effect of smoking on risk of severe COVID-19 (Clift et al., 2021).

In this study, there was no significant association found between smoking status with disease complications and outcomes when other variables such as age, gender and ethnicity were controlled. This insignificant association most probably due to several limitations such as recall and documentation biases on smoking history and COVID-19 clinical histories. This is consistent with the Scientific Brief Report published by the World Health Organization in June 2020, where hospital based studies had several limitations such as poor data quality and difficulty in collecting the history of smoking in an emergency context. On the other hand, during this initial pandemic wave in Malaysia, all patients diagnosed with COVID-19 were admitted to the hospital regardless of their severity as the country policy to curb the spread of this disease. In addition, the Mortality Rate and the Recovery Rate at that point of time were at 1.48% and 81.60% respectively. These rates indicate that the clinical management of COVID-19 patients in Malaysia is good and at par with other countries that were affected by the pandemic.

Despite the limitations that were mentioned earlier, this is the first study in Malaysia that investigated the association between smoking and COVID-19 infection using a large sample

size. Although current analysis still remains limited due to the quality of data collected, early findings from this study will support the current policy for tobacco control and allow for better prevention and treatment of smoking cessation in order to reduce the burden of serious complications of COVID-19 infection among smokers.

5. Conclusions

The findings from this study further support the current evidence that suggest association of smoking with COVID-19 complications and disease progression. As COVID-19 is still evolving, further research is warranted to determine the exact nature and magnitude of the association between smoking and COVID-19. Nevertheless, this pandemic brings the best opportunity for the public health to continue highlighting the benefits of quit smoking,

Declarations

Ethics: The study was registered with the National Medical Research Register (NMRR-20-580-54339) and approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia (KKM/NIHSEC/P20–706).

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1

Clinical Staging of COVID-19 Infection

Clinical staging	Features
I	Asymptomatic
II	Symptomatic, No pneumonia
III	Symptomatic, Pneumonia
IV	Symptomatic, Pneumonia, Requiring supplemental oxygen
V	Critically ill with multi-organ failure

*Based from Clinical Management of Confirmed COVID-19 Case in Adult and Paediatric Ministry of Health, Malaysia (updated 30th August 2021)

Table 2

Sociodemographic, clinical history and disease staging of COVID-19 cases at presentation to hospital according to smoking status

Variable	Total (n=5889)	Ever smoke (n=791)	Never smoke (n=5098)	p value
Age Group (n,%)				
< 30 years old	2486 (42.2%)	273 (34.5%)	2213 (43.4%)	< 0.001
31 to 50 years old	1919 (32.6%)	321 (40.6%)	1598 (31.3%)	
51 to 70 years old	1315 (22.3%)	167 (21.1%)	1148 (22.5%)	
Above 71 years old	169 (2.9%)	30 (3.8%)	139 (2.7%)	
Gender (n,%)				
Male	4221 (71.7%)	773 (97.7%)	3448 (67.6%)	< 0.001
Female	1668 (28.3%)	18 (2.3%)	1650 (32.4%)	
Ethnicity (n,%)				
Malay	3433 (58.4%)	434 (54.9%)	2999 (59.0%)	< 0.001
Chinese	391 (6.7%)	40 (5.1%)	351 (6.9%)	
Indian	135 (2.3%)	24 (3.0%)	111 (2.2%)	
Others	521 (8.9%)	96 (12.2%)	425 (8.4%)	

Non Malaysian	1396 (23.8%)	196 (24.8%)	1200 (23.6%)	
Comorbidities (n,%)				
Hypertension	931 (15.8%)	132 (16.7%)	799 (15.7%)	0.467
Diabetes	578 (9.8%)	97 (12.3%)	481 (9.4%)	0.013
Asthma	196 (3.3%)	15 (1.9%)	181 (3.6%)	0.016
Cardiac disease	190 (3.2%)	41 (5.2%)	149 (2.9%)	< 0.001
Chronic kidney disease	92 (1.6%)	13 (1.6%)	79 (1.5%)	0.843
Chronic pulmonary disease	32 (0.5%)	9 (1.1%)	23 (0.5%)	0.015
Liver disease	12 (0.2%)	1 (0.1%)	11 (0.2%)	0.604
Symptoms at presentation				
Respiratory symptoms				
Cough	1897 (32.2%)	240 (30.3%)	1657 (32.5%)	0.226
Having sputum	779 (13.2%)	114 (14.4%)	665 (13.0%)	0.291
Sore throat	841 (14.3%)	80 (10.1%)	761 (14.9%)	< 0.001
Runny nose	608 (10.3%)	69 (8.7%)	539 (10.6%)	0.112
Shortness of breath	312 (5.3%)	55 (7.0%)	257 (5.0%)	0.026
Gastrointestinal symptoms				
Diarrhea	298 (5.1%)	38 (4.8%)	260 (5.1%)	0.724
Nausea and vomiting	108 (1.8%)	6 (0.8%)	102 (2.0%)	0.015

Constitutional symptoms				
Fever	1737(29.5%)	194 (24.5%)	1543 (30.3%)	< 0.001
Myalgia	238 (4.0%)	20 (2.5%)	218 (4.3%)	0.020
Arthralgia	124 (2.1%)	17 (2.1%)	107 (2.1%)	0.927
Fatigue	202 (3.4%)	27 (3.4%)	175 (3.4%)	0.978
Headache	189 (3.2%)	19 (2.4%)	170 (3.3%)	0.166
Admission case classification (n,%)				
Asymptomatic	2956 (50.2%)	412 (52.1%)	2544 (49.9%)	0.042
Symptomatic	1859 (31.6%)	219 (27.7%)	1640 (32.2%)	
Pneumonia without hypoxia	801 (13.6%)	112 (14.2%)	689 (13.5%)	
Pneumonia with hypoxia	210 (3.6%)	35 (4.4%)	175 (3.4%)	
Critically ill	63 (1.1%)	13 (1.6%)	50 (1.0%)	
Duration of admission (mean, SD)	14.8 (9.2)	14.5 (8.3)	14.8 (9.3)	0.953

Table 3

Physical examination upon admission and investigations conducted to COVID-19 patients

Variable	Total (n=5889)	Ever smoke (n=791)	Never smoke (n=5098)	p value
Physical examination				
Blood pressure (mean, SD)				
Systolic	129.8 (17.6)	131.0 (17.5)	129.6 (17.6)	0.012
Diastolic	78.3 (11.8)	78.9 (11.5)	78.2 (11.8)	0.139
Pulse rate (mean, SD)	84.6 (13.8)	82.4 (14.1)	84.9 (13.7)	< 0.001
Respiratory rate (mean, SD)	19 (2.531)	19.193 (2.046)	19.184 (2.598)	0.533
Temperature (mean, SD)	36.8 (0.5)	36.7 (0.5)	36.8 (0.5)	0.018
Blood Investigation and Imaging				
Full blood count (mean, SD)				
White blood cells	7.8 (2.4)	8.1 (2.4)	7.7 (2.4)	< 0.001
Hemoglobin	14.4 (4.4)	14.9 (1.4)	14.3 (4.7)	< 0.001
Hematocrit	42.5 (8.9)	44.4 (5.8)	42.2 (9.3)	< 0.001
Platelet	270.0 (80.5)	264.5 (73.0)	270.9 (81.6)	0.147
Neutrophil count	4.7 (2.0)	4.9 (2.0)	4.6 (2.0)	0.002

Lymphocyte count	2.2 (0.9)	2.3 (0.9)	2.2 (0.9)	0.226
C-Reactive Protein (CRP) (mean, SD)	15.1 (41.1)	14.6 (43.6)	15.2 (40.6)	0.565
High CRP (≥5mg/dl) (n,%)	859 (27.7%)	104 (22.6%)	755 (28.6%)	0.008
Liver enzymes (mean, SD)				
ALT	35.5 (32.9)	38.8 (30.8)	35.0 (33.3)	< 0.001
AST	30.9 (26.0)	29.3 (15.6)	31.2 (27.3)	0.900
LDH (mean, SD)	246.0 (99.6)	235.4 (78.9)	247.8 (102.7)	0.002
Lymphopenia (<1 cell/uL) (n,%)	157 (4.5%)	11 (2.2%)	146 (4.9%)	0.008
Abnormal Chest X-ray (n,%)	1399 (31.0%)	222 (33.0%)	1177 (30.6%)	0.208

Table 4

Complications and outcomes of COVID-19 patients according to smoking status

Variable	Total (n=5889)	Ever smoke (n=791)	Never smoke (n=5098)	p value
Complications (n,%)				
Liver injury	393 (4.0)	66 (8.4)	327 (6.4)	0.043
Renal injury	236 (4.0)	45 (5.7)	191 (3.8)	0.010
Acute respiratory distress syndrome	136 (2.3)	28 (3.5)	108 (2.1)	0.013
Pleural effusion	27 (0.5)	5 (0.6)	22 (0.4)	0.437
Deep Vein Thrombosis	10 (0.2)	4 (0.5)	6 (0.1)	0.014
Seizure	7 (0.1)	3 (0.4)	4 (0.1)	0.022
Heart failure	19 (0.3)	5 (0.6)	14 (0.3)	0.099
Endocarditis	12 (0.2)	3 (0.4)	9 (0.2)	0.239
Cardiac arrhythmia	41 (0.7)	6 (0.8)	35 (0.7)	0.820
Cardiac arrest	38 (0.6)	8 (1.0)	30 (0.6)	0.167
Bacteremia	39 (0.7)	8 (1.0)	31 (0.6)	0.193
Admission to ICU (n,%)	193 (3.3)	34 (4.3)	159 (3.1)	0.083
Require oxygen (n,%)	474 (8.0)	71 (9.0)	403 (7.9)	0.303

Type of ventilation (n,%)				
Invasive	26 (3.3)	112 (2.2)	138 (2.3)	0.059
Non-invasive	49 (0.8)	6 (0.8)	43 (0.8)	0.806
Worst diagnosis outcome (n,%)				
No pneumonia	4211 (71.5)	545 (68.9)	3666 (71.9)	0.166
Pneumonia without hypoxia	1207 (20.5)	176 (22.3)	1031 (20.2)	
Pneumonia with hypoxia	303 (5.1)	40 (5.1)	263 (5.2)	
Critically ill	168 (2.9)	30 (3.8)	138 (2.7)	
Final outcome (n,%)				
Alive	5816 (98.9)	776 (98.1)	5040 (98.9)	0.073
Died	73 (1.2)	15 (1.9)	58 (1.1)	

Table 5

Logistic regression between smoking status, complications and outcomes of COVID-19 infection

Variable	Smoking status		Odd Ratio	p-value
	Ever smoke (n,%)	Never smoke (n,%)	(OR, 95% CI)	
Complications				
Liver Injury				
Yes	66 (8.4)	327 (6.4)	1.33 (1.01-1.74)	0.043
No	719 (91.6)	4782 (93.6)		
Renal Injury				
Yes	45 (5.7)	191 (3.8)	1.55 (1.10- 2.14)	0.010
No	744 (94.3)	4835 (96.2)		
Acute Respiratory Distress Syndrome				
Yes	28 (3.5)	108 (2.1)	1.69 (1.09-2.55)	0.013
No	763 (96.5)	4984 (97.9)		

Disease Outcomes				
Admission to ICU				
Yes	34 (4.3)	159 (3.1)	1.40 (0.94-2.01)	
No	757 (95.7)	4939 (96.9)		0.084
Require invasive ventilation				
Yes	26 (3.3)	112 (2.2)	1.51 (0.96-2.30)	0.061
No	765 (96.7)	4986 (97.8)		
Died				
Yes	15 (1.9)	58 (1.1)	1.68 (0.91-2.90)	0.076
No	776 (98.1)	5040 (98.9)		

Table 6

Subgroup analysis between current, former and non-smokers with complications and disease outcomes

Variable	Smoking status			Current vs non-smoker (p-value)	Current vs former smoker (p-value)
	Current smoker (n,%)	Former smoker (n,%)	Non-smoker (n,%)		
Complications					
Liver Injury					
Yes	36 (6.8)	30 (11.5)	327 (6.4)	0.733	0.025
No	493 (93.2)	231 (88.5)	4765 (93.6)		
Renal injury					
Yes	20 (3.8)	25 (9.6)	191 (3.8)	0.972	<0.001
No	509 (96.2)	236 (90.4)	4902 (96.2)		
Acute Respiratory Distress Syndrome					
Yes	15 (2.8)	13 (5.0)	108 (2.1)	0.287	0.125
No	514 (97.2)	248 (95.0)	4984 (97.9)		
Disease Outcomes					
Admission to ICU					
Yes	17 (3.2)	17 (6.5)	159 (3.1)	0.905	0.032
No	512 (98.7)	245 (93.5)	4939 (96.9)		
Require invasive ventilation					

Yes	12 (2.3)	14 (5.3)	112 (2.2)	0.915	0.022
No	517 (97.7)	248 (94.7)	4986 (97.8)		
Died					
Yes	7 (1.3)	8 (3.1)	58 (1.1)	0.704	0.093
No	522 (98.7)	254 (96.9)	5040 (98.9)		

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: